Migraine

Henry H. Chen, MD[a,*], Kelly M. Heath, MD[b,c], Palak R. Patel, MD[a]

KEYWORDS

• Migraine • Headache • Trigeminovascular • Vasodilation • Botulinum toxin
• Mindfulness

KEY POINTS

- Migraine is a recurrent condition that can have a significant impact on quality of life, often interfering with daily activities.
- Migraine pathophysiology: vascular and neurovascular theories; cortical spreading depression increases excitability and glutamate release, linked to auras.
- Migraines progress through prodrome, aura, headache, and postdrome; diagnosis relies on history, symptoms, and ruling out secondary causes.
- Acute treatment: NSAIDs, triptans, antiemetics, ergot derivatives, CGRP antagonists. Preventive options: beta-blockers, anticonvulsants, antidepressants, CGRP monoclonal antibodies.
- Non-pharmacologic approaches, like lifestyle modifications, biofeedback, and cognitive-behavioral therapy, can complement pharmacotherapy.

EPIDEMIOLOGY

Migraine is a neurovascular disorder that affects people across the globe. It is the second leading cause of disability worldwide, falling behind low back pain.[1] The current estimate for global migraine prevalence is about 14%. Women tend to have a greater global migraine prevalence when compared to men, 18% compared to 10%. Migraine makes up about 5% of global ill health, measured in years lived with disability.[1,2]

PATHOGENESIS

Current literature and understanding of the pathophysiology of migraine remain incomplete. However, much of the research has described 2 main theories. This

[a] Department of Physical Medicine and Rehabilitation, Hospital of the University of Pennsylvania, 1800 Lombard Street, Philadelphia, PA 19146, USA; [b] Department of Physical Medicine and Rehabilitation, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA; [c] Rehab Medicine Service, Corporal Michael J. Crescenz VA Medical Center, 3900 Woodland Avenue, Mail Stop #117, Philadelphia, PA 19104, USA
* Corresponding author. 1800 Lombard Street, Philadelphia, PA 19146.
E-mail address: Henry.Chen@pennmedicine.upenn.edu

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Abbreviations	
BOTOX	onabotulinumtoxinA
CGRP	calcitonin gene-related peptide
COX	cyclooxygenase
CSD	cortical spreading depression
ICHD	International Classification of Headache Disorders
NSAID	non-steroidal anti-inflammatories drug
PACAP	pituitary adenylate cyclase-activating peptide
SNRI	serotonin and norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
TCA	tricyclic antidepressant

includes the vascular theory and the neurovascular theory. The latter incorporates neuropeptides, the trigeminal system, and neurogenic inflammation.

The vascular theory suggests that migraines occur due to vasodilation of meningeal arteries. An increased level of nitric oxide produced from the endothelium of meningeal and dura blood vessels are the primary reason for vasodilation.[3] Serotonin also plays a role in the vascular theory, particularly acting as a vasoconstrictor capable of reducing migraine headaches. The primary receptors include 5-HT_{1B} and 5-HT_{1D}.[4,5] Also implicated is 5-HT_{1F}, which acts more as a modulator than a vasoconstrictor. It can prevent further pain signaling and cascades that contribute to migraines.[6]

The neurovascular theory includes vasodilation as a mechanism for migraine but expands on it through the relationship between neuropeptides and inflammation. The systems involved in this theory include the trigeminal system, meningeal blood vessels, the hypothalamus, and the thalamus. One central phenomenon in this theory is cortical spreading depression (CSD). Its role is primarily used to describe auras that are associated with migraine.

CSD is a slow-spreading wave that affects glial and neuronal cells. The mechanism is tied to intracellular and extracellular ion changes, particularly depolarization, which enhances neuronal excitability.[7] Glutamate via the NMDA receptor has also been shown to contribute to CSD and is elevated in those with migraine.[8] CSD sensitizes the trigeminal system, releasing several peptides that cause vasodilation in cerebral blood vessels.

Some important neuropeptides include calcitonin gene-related peptide (CGRP), pituitary adenylate cyclase-activating peptide (PACAP), and histamine. CGRP acts on the CLR/RAMP1 receptors and directly causes meningeal vasodilation by activating a signaling cascade.[9] PACAP also causes vasodilation of meningeal arteries.[10] Histamine causes meningeal nociceptor sensitization, as well as vasodilation.[11] The hypothalamus and thalamus also play a role in migraine. The hypothalamus through its interaction with the thalamus and superior salivatory nucleus increases the production of nitric oxide leading to meningeal vasodilation.[12] Other research not discussed here involves a genetic component to migraine, as well as sex-linked hormones.

History

Patients presenting with migraine will often describe episodes with chronologic symptoms, defined into 4 phases (**Table 1**).

The International Classification of Headache Disorders (ICHD)-3 outlines criteria that align with the symptoms described in these phases, which can help guide history collecting and diagnosis. Other questions can also include the timing of the headache,

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Table 1
Migraine phases

Phase	Name	Symptoms	Timing
First	Prodrome	Yawning, photophobia, neck stiffness, phonophobia	24–48 h before the headache
Second	Aura	25% report visual symptoms like scintillating scotomas or reduced visual fields, or sensory symptoms like	Usually <60 min
Third	Headache	Intense, unilateral, throbbing pain often with associated nausea, photophobia, phonophobia, rhinorrhea, or lacrimation	Varies – a few hours to several days
Fourth	Postdrome	Movement reproducing pain in a similar area as migraine. Additional symptoms like exhaustion, dizziness	Up to 24 h after headache

Data from Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018;38(1):1-211. https://doi.org/10.1177/0333102417738202.

how it changes over time, and if they have tried any medications. A helpful mnemonic is POUND—pulsating, duration of 4 to 72 h, unilateral, nausea, disabling—can be used in assessing symptoms.[13] In addition, patients should be asked the number of days per month on which headache occurs as this distinguishes its classification as episodic or chronic. Chronic migraine is defined by 15 or more headache days per month, which include 8 or more migraine days a month for over 3 mo duration.[14]

Patients may report triggers like stress, menstrual cycles, hunger, weather changes, sleep, odors, or certain foods. One should ask about family history, as the risk of migraine is increased trifold if a patient has a relative with migraines.[14]

When taking a headache history, it is crucial to identify "red flags" that might suggest a more serious underlying cause. Be sure to ask about systemic symptoms, such as fever or weight loss, as well as neurologic symptoms like sudden vision loss or weakness.[14]

Evaluation

Patients presenting with acute headache concerning for migraine should undergo a comprehensive examination to ensure secondary headaches are also ruled out. Vital signs should be obtained to assess for febrile illness, abnormal heart rate or rhythm, or hypertension/hypotension. Examiners can palpate a patient's scalp, cervical muscles, and jaw for tenderness. A complete neurologic examination should be performed, including a funduscopic examination to check for papilledema or other abnormalities. Cranial nerves should be tested with special attention to optic, oculomotor, trochlear, and abducens nerves. Special tests like Kernig's and Brudzinski's signs should also be performed to assess for meningeal irritation.[15]

Kerning's sign is performed by flexing a patient's hips and knees to 90° while supine, and then passively extending 1 knee. A positive Kerning's sign is resistance or pain when the knee is extended beyond 135°. Brudzinski's neck sign is again with the patient supine, and the examiner passively flexes their neck and a positive sign is if there is reflex flexion of the patient's hips and knees. Both signs are based on stretching the nerve roots, and if inflamed meninges are present, then the patient would have reflexes to reduce the tension. While these signs have low sensitivity, they both have

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high specificity, and further workup should be pursued for meningitis if both are present.[16]

A complete neurologic examination of mental status, cranial nerves, strength, sensation, reflexes, cerebellar signs, and gait will ensure secondary headaches due to a neurologic insult are not missed. Patients with auras may experience somatosensory symptoms, but they should be transient and not result in persistent motor weakness or cerebellar signs.[15]

CLASSIFICATION OF HEADACHE DISORDERS

In 1985, the International Headache Society sought to classify headaches. This led to the first edition of the ICHD published in 1988. Now this document has become a standard of use clinically and in research. The third edition, of ICHD was published in 2018.[17]

Primary headaches are diagnosed clinically; however, neurochemical markers, genetics, and imaging are being studied to help diagnose primary headaches.[17]

When using the ICHD-3 it is important to understand how the document is organized. There are 14 different main categories of headaches, and an appendix contains relatively new diagnoses or those that have been validated. Within each category are different subdivisions, denoted by a number following a decimal. For example, 4.5.3—probable cold-stimulus headache. The 4 stands for other primary headache disorders; the 5 stands for cold-stimulus headache; and the 3 stands for probable cold-stimulus headache. Probable is used when a headache type is missing but one criteria.

The ICHD-3 can be found on their website – ihs-headache.org under “resources”, then “guidelines”.[17]

DIAGNOSIS

Migraine is considered a primary headache under ICHD-3. They are broken up into those without aura, those with aura, chronic migraine, complications of migraine, probable migraine, and episodic syndromes that may be associated with migraine.

The diagnostic criteria for migraine without aura are also composed of many parts. There must be at least 5 attacks, these attacks should last 4 to 72 h and must have at least nausea/vomiting or photophobia and phonophobia. The characteristics of the migraine must include 2 out of 4 of the following: unilateral in location, pulsating in quality, moderate or severe intensity, and aggravated by routine physical activity.[14] See **Box 1** for a complete breakdown.

Migraine with aura requires less frequency, develop gradually, and with various neurologic symptoms. The criteria for migraine with aura can be found in **Box 2**. Of note, this new way of classifying migraine with aura is better at distinguishing it from transient ischemic attacks.[18]

Visual auras are the most common, followed by sensory symptoms, such as pins and needles. Numbness may also occur. Symptoms like aphasia are rarer. When multiple symptoms occur, they usually follow in succession. Auras typically last 1 h, but motor symptoms can be longer.[14]

A subgroup of migraine with aura is the migraine with typical auras. These include auras with visual, sensory, and speech symptoms. However, do not present with motor, brainstem, or retinal symptoms.[14]

Migraines with motor weakness are labeled as hemiplegic migraine. Migraine with brainstem aura should have at least 2 of the following—dysarthria, vertigo, tinnitus, hyperacusis, diplopia, ataxia not attributable to any sensory deficit, decreased level of consciousness, and no motor or retinal symptoms. These symptoms are reversible and should not be accounted for another ICHD-3 criteria.[14]

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Box 1
Migraine without aura

A. At least 5 attacks fulfilling criteria B-D

B. Headache attacks lasting 4-72 h (when untreated or unsuccessfully treated)

C. Headache has at least 2 of the following 4 characteristics:
   1. Unilateral location
   2. Pulsating quality
   3. Moderate or severe pain intensity
   4. Aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)

D. During headache at least 1 of the following:
   1. Nausea and/or vomiting
   2. Photophobia and phonophobia

D. Not better accounted for by another ICHD-3 diagnosis.

Data from (Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. *Cephalalgia*. 2018;38(1):1-211. https://doi.org/10.1177/0333102417738202.)

Retinal migraines are rarer and include visual disturbances, such as scintillations, scotoma, or blindness associated with a migraine headache. These symptoms must be confirmed through either a clinical visual examination or the patient's drawing of a monocular field defect. The duration and presentation of the headache must include 2 of the following—spreading gradually over more than 5 min, lasting 5 to 60 min, and followed within 60 min by a headache.[14]

Chronic migraine is characterized by the number of headache and migraine days, as often, patients with very frequent migraines also have inter-ictal headaches that are

Box 2
Migraine with aura

A. At least 2 attacks fulfilling criteria B and C

B. One or more of the following fully reversible aura symptoms
   1. Visual
   2. Sensory
   3. Speech and/or language
   4. Motor
   5. Brainstem
   6. Retinal

C. At least 3 of the following 6 characteristics
   1. At least 1 aura symptom spreads gradually over $\geq$5 min
   2. Two or more aura symptoms occur in succession
   3. Each aura symptom lasts 5 to 60 min
   4. At least 1 aura symptom is unilateral
   5. At least 1 aura symptom is positive[a]
   6. The aura is accompanied, or followed within 60 min, by a headache

D. Not better accounted for by another ICHD-3 diagnosis

[a]Positive symptoms are pins and needles and scintillations.

Data from (Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. *Cephalalgia*. 2018;38(1):1-211. https://doi.org/10.1177/0333102417738202)

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not migraine. The total number of headache days being more than 15 in a month and for more than 3 mo. Eight or more headache days within the month should have the features of migraine headaches. Further details on the criteria can be found in **Box 3**. Tension headaches are included in the criteria because it can be difficult to differentiate the headaches when they occur so frequently. Of note, medication overuse headache, 8.2, can confound chronic migraine and should be investigated when making the diagnosis of chronic migraine.[14]

Complications of migraine include symptoms with prolonged duration or trigger a separate neurologic event. For example, status migrainosus is a debilitating migraine attack lasting for more than 72 h. Other examples include migraine aura-triggered seizure, migranous infarction, and persistent aura without infarction.[14]

There are also episodic syndromes that may be associated with migraines that will not be discussed extensively. Some examples include recurrent gastrointestinal disturbances, cyclic vomiting syndrome, abdominal migraine, benign paroxysmal vertigo, and benign paroxysmal torticollis. Most of these symptoms occur in children, although adults have been found to develop these symptoms as well.[14]

DIFFERENTIAL DIAGNOSIS

When diagnosing migraine some differentials to consider include secondary headaches, such as headaches attributed to a substance or its withdrawal, medication overuse, meningitis, encephalitis, headaches attributed to hypertensive crisis, cervicogenic headaches, trigeminal neuralgia, giant cell arteritis, subarachnoid hemorrhage, and dissection syndromes. Two primary headaches to consider are cluster headaches and tension headaches.[19]

A tension headache can occur frequently or infrequently, typically lasting from 30 min to 7 d. It should include 2 of the following: bilateral location, pressing or tightening quality, mild to moderate intensity, and not aggravated by routine physical activity. There should be no nausea, vomiting, photophobia, or phonophobia present.[14]

A cluster headache is diagnosed when 5 or more attacks of severe pain occur, typically in the orbital, supraorbital, or temporal region. The headaches last from 15 min to

Box 3
Chronic migraine

A. Headache (migraine-like or tension-type-like) on ≥15 d/mo for greater than 3 mo, and fulfilling criteria B and C.

B. Occurring in a patient who has had at least 5 attacks fulfilling criteria B–D for Migraine without aura and/or criteria B and C for Migraine with aura.

On 8 d/mo for greater than 3 mo, fulfilling any of the following:
1. Criteria C and D for Migraine without aura
2. Criteria B and C for Migraine with aura
3. Believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative)

D. During headache at least one of the following:
   1. Nausea and/or vomiting
   2. Photophobia and phonophobia

D. Not better accounted for by another ICHD-3 diagnosis.

Data from (Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia 2018;38(1):1-211. https://doi.org/10.1177/0333102417738202)

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3 h and occur once every other day to 8 times a day. At least 1 of the following symptoms should also be present during the headache: lacrimation, conjunctival injection, nasal congestion, rhinorrhea, eyelid edema, forehead/facial sweating, miosis/ptosis, and a sense of restlessness and agitation.[14]

When making a diagnosis of migraine or any primary headache disorder, one has to consider possible secondary causes. This is true for any headaches that occur in close temporal relation to a known secondary condition that causes headaches. An example would be headaches occurring after a traumatic brain injury. A primary headache may be diagnosed if the patient had pre-existing headaches before the secondary condition occurred.[14]

CONSIDERATIONS

The decision to take up an investigation for secondary headache can often be difficult as is requires considerable clinical judgment. However, presence of certain "red flags" may suggest a secondary cause. The SNNOOP10 lists 15 red flags that could point more toward a secondary headache than a primary headache. However, this list has not been tested or verified through any large-scale study. **Box 4** shows a list of red flags.[20]

Green flags point more toward a primary headache diagnosis. The complete list of green flags is presented in **Box 5**. These green flags have not been heavily studied and utility may be limited. Most of the information is based on expert opinion.[21]

MANAGEMENT

The treatment of migraine involves both acute and prophylactic strategies. Recent advances in understanding the vascular and neurovascular theories of migraine have introduced new treatment options.

Acute (abortive) treatments include non-steroidal anti-inflammatories drugs (NSAIDs), triptans, anti-emetics, ergot derivatives, and newer options like the ditans and CGRP antagonists.

Box 4
Red flags

Sign or symptom

1. Systemic symptoms including fever
2. Neoplasm in history
3. Neurologic deficit or dysfunction (includes decreased consciousness)
4. The onset of headache is sudden or abrupt (thunderclap headache)
5. Older than 50 y of age
6. Pattern change or recent onset of headache
7. Positional change
8. Precipitated by sneezing, coughing, or exercise
9. Papilledema
10. Progressive headache and atypical presentations
11. Pregnancy or puerperium
12. Painful eye with autonomic features
13. Post-traumatic onset of headache
14. Pathology of the immune system or medical immunosuppression
15. Painkiller overuse or new drug at onset of headache

(*Data from* Do TP, Remmers A, Schytz HW, et al. Red and orange flags for secondary headaches in clinical practice: SNNOOP10 list. Neurology 2019;92(3):134–44. https://doi.org/10.1212/WNL.0000000000006697)

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Box 5
Green flags

Sign or symptom
1. Current headache has been present during childhood
2. The patient has headache-free days
3. The headaches occur in temporal relation to the menstrual cycle
4. Close family members have the same headache phenotype
5. Headache occurred or stopped more than 1 week ago.

(*Data from* Pohl H, Do TP, García-Azorín D, et al. Green Flags and headache: a concept study using the Delphi method. Headache 2021;61(2):300–09. https://doi.org/10.1111/head.14054.)

- *NSAIDs* (e.g. naproxen, aspirin, celecoxib, ibuprofen, and diclofenac) act as anti-inflammatories and analgesics. They work by inhibiting cyclooxygenase (COX), which in turn reduces prostaglandin production. COX-1 and COX-2 play a role in peripheral sensitization within the trigeminovascular system, contributing to central sensitization.[22] These drugs are typically used for mild or moderate migraines, especially when nausea or vomiting is not present.[19]
- *Triptans* target $5HT_{1B/1D}$ receptors and act as vasoconstrictors. Due to their generalized vasoconstrictive effect on cerebral and coronary vessels, triptans are considered contraindicated in patients with ischemic stroke, ischemic heart disease, poorly controlled hypertension, angina, pregnancy, and hemiplegic or basilar migraines. Key side effects include severe liver impairment, prolonged QT interval, peripheral ischemia, and the risk of serotonin syndrome.[23] Sumatriptan, in particular, offers multiple routes of administration, including oral tablets, nasal spray, nasal powder, and subcutaneous injection.[24]
- *Ditans*, such as Lasmiditan, have been recently U.S. Food and Drug Administration (FDA)-approved and act on the $5HT_{1F}$ receptor, offering the advantage of treating migraines without causing vasoconstriction.[6] However, ditans act centrally and have been shown to impair driving, so patients should avoid driving or operating machinery for 4 h after a dose.[25]
- *Anti-emetics* like the D2 dopamine receptor antagonists—metoclopramide and prochlorperazine—are effective for migraines, likely due to their ability to suppress trigeminovascular activation.[26]
- *CGRP antagonists* represent a newer class of drugs developed from insights into the neurovascular theory of migraine. CGRP plays a role in the pain signaling cascade, leading to meningeal vasodilation. Rimegepant and Ubrogepant are 2 examples used as second-line options for treating migraine. While triptans have shown slightly superior efficacy for pain relief at the 2-h mark, CGRP antagonists tend to have fewer side effects.[27] Common side effects include nausea for Rimegepant, while Ubrogepant may cause sedation.[28]
- *Ergot derivatives* like dihydroergotamine and ergotamine tartrate are also used in acute migraine treatment. Their mechanism of action is not entirely understood but they act on $5HT_{1B/1D}$ receptors, as well as dopamine and adrenergic receptors. As a result, their side effect profile is similar to that of triptans, and they are contraindicated in patients with coronary artery disease, stroke, or peripheral vascular disease.[29] They can also pose a risk for serotonin syndrome.[30]

Neuromodulation techniques have emerged as additional options for migraine management. Transcutaneous supraorbital nerve stimulation has been shown to reduce migraine intensity, while transcranial magnetic stimulation may help in chronic migraine and can be considered a second-line treatment.[31] Other techniques include

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non-painful remote electric neurostimulation and peripheral nerve blocks targeting the occipital plexus and sphenopalatine ganglion.[32]

Prophylactic treatments or preventive treatments aim to reduce the frequency, severity, and duration of acute migraines. These treatments are often considered when acute therapies are contraindicated or ineffective. They may also be recommended for certain migraine subtypes, such as hemiplegic migraine, migrainous infarction, persistent aura without infarction, or migraine with brainstem aura. Many preventive treatments were originally developed for other conditions, such as hypertension, depression, or epilepsy.

- *Anti-hypertensives*: Beta-blockers are particularly effective for preventing migraines. Metoprolol, propranolol, timolol, and nadolol have shown efficacy, with nadolol being the only one that does not act centrally. The neurogenic mechanism behind beta-blockers effectiveness in migraine prevention is thought to involve the blockade of beta-1 receptors, which reduces sympathetic nervous system excitability.[33] Other potential mechanisms include thalamic inhibition and nitrous oxide blockade. These medications are contraindicated in patients with heart block, syncope, or asthma.[34]
- *Antidepressants*: Several classes of antidepressants are used to prevent migraines, including tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and serotonin and norepinephrine reuptake inhibitors (SNRIs). Common examples include amitriptyline (TCA), fluoxetine (SSRI), and venlafaxine (SNRI). While the exact mechanism by which antidepressants prevent migraine is unclear, amitriptyline acts as a mixed SNRI and may prevent CSD through its antihistamine effects. Fluoxetine increases serotonin levels as an SSRI, while venlafaxine raises SNRI levels through its SNRI action. The main side effects of amitriptyline include dry mouth and somnolence.[34] SSRIs and SNRIs can cause sexual dysfunction, and both drug classes pose a risk of serotonin syndrome.[35]
- *Anti-epileptic medications*: Topiramate and divalproex sodium are commonly used to prevent migraines. Though the exact mechanism is unclear, topiramate blocks sodium and calcium channels, inhibits excitatory neurotransmission, and reduces CGRP secretion from trigeminal neurons, all of which may contribute to migraine prevention. Valproate works similarly by blocking excitatory ion channels and enhancing Gamma-Aminobutyric Acid (GABA) mediated inhibition, and it may also reduce CGRP expression in the brain. Side effects of topiramate include nausea, vomiting, weight loss, dizziness, and fatigue. Valproate can cause weight gain, abdominal pain, nausea, headaches, and hair loss. Valproate is contraindicated in pregnancy and patients with hepatic dysfunction.[34,35]
- *Monoclonal antibodies targeting CGRP*: A newer class of drugs specifically designed for migraine prevention includes monoclonal antibodies that target CGRP or its receptors. These medications include erenumab, fremanezumab, galcanezumab, and eptinezumab. Erenumab targets the CGRP receptor, while the others target CGRP ligands. These drugs are typically administered through monthly subcutaneous injections, except for eptinezumab, which is given intravenously. The adverse effects are mostly mild and injection-site-related, such as erythema or pruritus.[36]

Botulinum Toxin Injections for Chronic Migraine

For patients with chronic migraine, the PREEMPT trial validated the use of onabotulinumtoxinA (Botox) injections as a prophylactic treatment, finding a reduction in

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headache days and symptoms, headache-related disability, and quality of life when compared to placebo.[37,38]

These trials resulted in a PREEMPT protocol with 31 sites of 5 units of Botox each with a total of 155 units (**Table 2** and **Fig. 1**).

This procedure is fairly well-tolerated, with adverse events of neck pain in 6.7%, muscular weakness in 5.5%, eyelid ptosis in 3.3%, and muscular pain in 2.2% compared to 2.2%, 0.3%, 0.3%, and 0.7% in placebo, respectively.[39]

Complementary and Integrative Medicine

Mindfulness

Various studies have reviewed the effects of meditation, yoga, and tai chi for the prevention and treatment of migraine. An 8-w, standardized mindfulness-based stress reduction program developed by Dr Jon Kabat-Zinn served as the intervention in various studies, finding decreased pain intensity, improved quality of life, and emotional dimension of pain, disability, and distress. Another study looked at stress coping skills and cortical activity, finding those with episodic migraine had higher rates of negative coping skills with the associated cortical stress processing when matched to healthy individuals and meditators. Yoga has also been shown to be helpful, where some studies found a decrease in headache frequency and severity compared to those who used medication alone. Tai chi has less research, but some evidence has shown a decrease in migraine days as well. While the research is not all generalizable and has study limitations, incorporating mindfulness techniques may help patients with the pain-psychologic aspect of migraine and can be offered as adjuvant options as they are generally considered safe.[40]

Supplements

The American Headache Society released updated evidence-based guidelines on the use of dietary supplements for the prevention of migraine episodes. **Table 3** presents an overview.[41]

Previously, studies on butterbur found evidence for its use in migraine prevention, but some formulations were hepatoxic, so it is no longer recommended due to safety concerns. Furthermore, supplements on the market are not regulated by the US Food and Drug Administration, so users should always practice caution.[41]

Table 2
Botulinum toxin injection sites

Muscle (Site on Image)	Total Units	Number of Sites
Corrugator (A)	10	2
Procerus (B)	5	1
Frontalis (C)	20	4
Temporalis (D)	40	8 (4 on each side)
Occipitalis (E)	30	6
Cervical Paraspinals (F)	20	4
Trapezius (G)	30	6

(*Data from* Wang YF. Chapter 7 - OnabotulinumtoxinA injection in the treatment of chronic migraine. In: Wang SJ, Lau CI, eds. Progress in brain research. Vol 255. Update on emerging treatments for migraine. Elsevier .2020:171–06. https://doi.org/10.1016/bs.pbr.2020.05.013)

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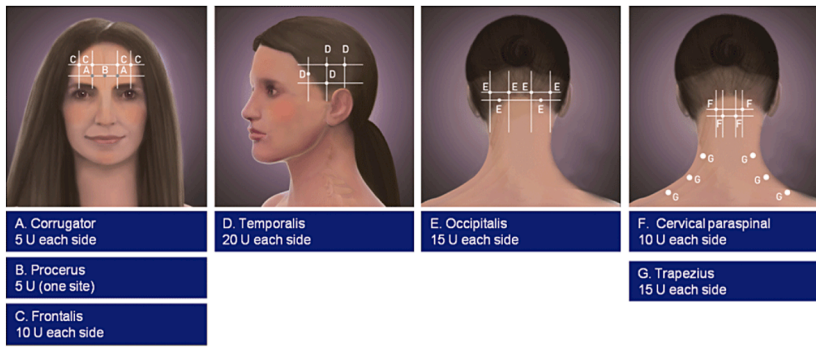

Fig. 1. Injection sites according to the PREEMPT trial (*Source* Wang YF. Chapter 7 - OnabotulinumtoxinA injection in the treatment of chronic migraine. In: Wang SJ, Lau CI, eds. Progress in Brain Research. Vol 255. Update on Emerging Treatments for Migraine. Elsevier; 2020:171–06. https://doi.org/10.1016/bs.pbr.2020.05.013 Previously published in Elsevier.)

Manual therapy

Physical therapy modalities, osteopathic manipulative treatment, and chiropractic therapy have shown some benefits in reducing headache-related disability and symptoms with treatments focusing on myofascial release, massage, trigger point compression, and/or stretching. These modalities can be helpful added treatments, but caution should be used with high-velocity techniques and their risk of cervical dissection.[40]

Though a trigger for some, aerobic exercise can also help reduce migraine frequency, duration, and pain.[40]

Table 3
Supplements

Supplement	Proposed Mechanism	Dose	Side Effects
Magnesium	Energy production, cortical spreading depression	600 mg daily	Diarrhea. This can be reduced with different formulations.
Riboflavin (Vitamin B2)	Mitochondrial energy production	400 mg daily	Urine discoloration, diarrhea
Feverfew – *(Parthenolide - active agent)*	Vascular smooth muscle relaxation	50–300 mg daily	Nausea, bloating, aphthous ulcers. Avoid in pregnancy – can cause uterine contractions
Coenzyme Q10 (CoQ10)	Energy production, mitochondrial integrity	300 mg daily	Insomnia, fatigue, nausea, diarrhea
Melatonin	Pituitary hormone to regulate circadian rhythm	3 mg 30 min before bedtime	Dizziness, headache, nausea, sleepiness

(*Data from* Patient-Education-Kit-for-Migraine-Final-Supplements-11–27–22-Revision.pdf. Accessed October 22, 2024. https://americanheadachesociety.org/wp-content/uploads/2022/12/Patient-Education-Kit-for-Migraine-Final-Supplements-11-27-22-Revision.pdf.)

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Acupuncture can also be a very valuable treatment for some. A Cochrane review of nearly 5000 participants found similar benefits to prophylactic medications and was superior to sham acupuncture. One study used MR spectroscopy pre-acupuncture and post-acupuncture treatment and found biochemical changes in the bilateral thalamus that were associated with decreased headache intensity scores, suggesting that acupuncture can modulate the pain perception pathway.[40]

SUMMARY

Migraine is a complex neurovascular disorder that occurs over hours. Women tend to have a greater global prevalence than men. Due to its duration, classifying which phase a patient is in can help with management. The examination can be daunting because of the wide differentials. Nevertheless, a thorough examination and utilizing tools such as "green" or "red" flags may help provide an outline when performing the examination. Although many medications have been used and developed for the treatment of migraine, it is important to be aware of the complementary and integrative treatment options available. Technology involving neuromodulation techniques may interest certain patients with adverse side effects from medications. Many of the prophylactic medications also provide other benefits and should be reviewed when considering a medication to start. Overall migraine is becoming better understood and treatments targeting a direct pathway during its progression are being made.

CLINICS CARE POINTS

- Women tend to have a greater prevalence and the global burden is only second to lower back pain. Therefore, accurate diagnosis and treatment are pivotal in reducing disease burden.
- Migraines progress over hours and through different phases. Understanding how patients respond to different treatments during specific phases can help improve 2-h pain relief.
- The differential diagnoses for migraine is extensive. A thorough history and examination are critical when assessing headaches in general. The use of "red" and "green" flags can help tailor the examination. Referring to ICHD-3 can be helpful as well.
- Many treatment options exist for migraine allowing for flexibility and patient-centered treatment regimens. Preventive medications can help with depression, seizures, or hypertension. Common side effects among the acute treatments include serotonin syndrome, drowsiness, and vasoconstriction. Complementary medications and neuromodulation techniques are beneficial and should be utilized.

DISCLOSURES

The contents of this work do not represent the views of the Department of the Veterans Affairs or the United States Government. The authors have nothing to disclose.

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